

Several of the identified genes such as *PTGES* and *FRZB* were previously found to mark OA in expression analyses and/or genetic association studies. Remarkably, we identified several genes which regulate nerve growth processes to be up-regulated in the OA affected areas. This finding raises the question whether increasing pain signals at OA lesions may confer risk to joint replacement surgery.

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GENETIC POLYMORPHISMS OF TUMOR NECROSIS FACTOR ALPHA GENE AND SUSCEPTIBILITY TO HAND OSTEOARTHRITIS IN FINNISH WOMEN

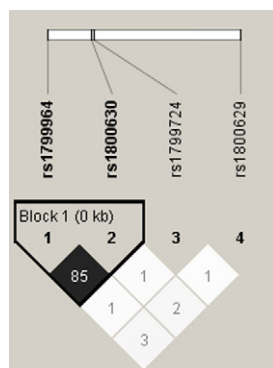
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Purpose: Osteoarthritis (OA) is a common disease characterised by degeneration of the cartilage of synovial joints. Available evidence suggests that genetic factors may play a major role in the etiology of OA. Since Tumor necrosis factor alpha (TNFα) has been shown to be produced more in OA cartilage than in normal cartilage, it is a good candidate for these genetic factors. We examined this by studying the role of four single nucleotide polymorphisms (SNPs) (rs1799964 "-1031", rs1800630 "-863", rs1799724 "-857" and rs1800629 "-308") in TNFα gene and their haplotypes in the individual susceptibility to hand OA in Finnish women.

Methods: Bilateral hand radiographs of 543 Finnish female dentists and teachers aged 45–63 years and living in the Helsinki metropolitan region were examined and classified for the presence of OA using a modified Kellgren-Lawrence (K-L) system and reference images. Hand OA was defined as at least mild (K-L > 2) symptomatic distal interphalangeal (DIP) hand OA in at least 2 finger joints (symptDIP OA 2+ > 2). The genotypes were determined by PCR-based methods. Data regarding other risk factors were collected by questionnaire. Association between the genotypes/haplotypes and hand OA were studied by logistic regression with SPSS statistical package Version 18.0. Haplotypes were analysed with Haploview program and reconstructed with PHASE

Results: According to power calculations, this study had 80% power to detect ORs from 2.7 to 4.0 depending on the minor allele frequency (6–18%), based on a two-sided alpha of 0.05.

The prevalence of symptDIP OA 2+ > 2 was 9%, (6.8% in dentists, 11.7% in teachers). The genotype frequencies were in Hardy-Weinberg equilibrium in all studied polymorphic loci. An association was found between the TNFα -1031 and -863 loci's minor allele carriage (C-allele in -1031 and A-allele in -863) and symptDIP OA 2+ > 2 when adjusted for age, occupation and BMI. The minor allele in -1031 locus posed a borderline significant risk in total sample (OR 1.76 95% CI 0.95–3.29). When stratified by occupation an almost 3-fold risk (OR 2.81, 95% CI 1.06–7.45) was seen in dentists whereas no statistically significant association was seen in teachers (OR 1.30, 95% CI 0.57–2.95). Similarly, carriage of the minor allele in -863 locus posed an over 2-fold risk in total sample (OR 2.13, 95% CI 1.14–4.00), and when stratified by occupation the risk was over 3-fold in dentists (OR 3.40, 95% CI 1.27–9.13) whereas no statistically significant association was seen in teachers (OR 1.56, 95% CI 0.68–3.56).



Haplotype analyses revealed a LD between the TNFα -1031 and -863 loci (D' 1.0; r^2 0.86). The most common haplotype was TC (82%), followed by CA (17%) and CC (2%). The haplotype analysis gave similar results to the genotype analyses; the CA-haplotype showed association to symptDIP OA 2+ > 2 when adjusted for age, occupation and BMI (OR 1.80 95% CI 1.06–3.08). When stratified by occupation the dentists had an over 2-fold

risk (OR 2.29 95% CI 1.01–5.20) whereas no significant risk was seen in teachers (OR 1.54 95% CI 0.76–3.13).

Conclusions: Our results suggest that the TNFα gene polymorphisms may play a role in the etiology of hand OA.

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GENOME-WIDE ASSOCIATION STUDY TO IDENTIFY NEW GENES AND PATHWAYS CONFERRING RISK TO OA SUSCEPTIBILITY IN MULTIPLE JOINT LOCATIONS AS DEFINED IN THE GARP STUDY

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Purpose: Identify, by genome wide association (GWAS), common OA susceptibility loci conferring risk to OA at multiple joint locations as defined in the GARP study.

Methods: A genome wide scan was performed by applying the Illumina Human660W in the GARP study (N = 380) and random controls (N = 1670). The GARP study consists of sibling pairs with symptomatic OA at multiple joint locations at relative young age (40–70 yrs). This relatively severe phenotype with familial background may help to stratify OA into a genetically homogeneous subset, thereby enhancing power and allowing identification of variants with larger impact. Putative OA susceptibility loci with P -values $\leq 10^{-5}$ were replicated both *in silico* (3 datasets for multiple joint OA, total N = 796 cases and 44088 controls) and by *de novo* genotyping (N = 400). Pathway analysis was performed with the top 200 loci of the GARP genome wide scan by applying the Database for Annotation, Visualization and Integrated Discovery (DAVID).

Results: Our analyses resulted in 3 loci at 6q21 (106 Mb), 7q35 (146 Mb) and 15q26 (91 Mb) that confer consistent risk to OA at multiple joint locations with an overall P -value $< 10^{-4}$ in the meta-analysis. Pathway analysis indicated a significant involvement of genes expressed during development.

Conclusions: Although 3 loci showed consistent association to OA at multiple joint locations, none passed the genome-wide significance level (P -value $< 10^{-8}$). Further analyses are necessary to confirm whether these putative loci confer risk to our specific OA phenotype. In addition, we would like to investigate whether these loci also play a role in more common OA subtypes by analyses in much larger datasets. Our pathway analyses supported the hypothesis of OA being a disease with an early developmental component.

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COMMON VARIANTS IN SKELETAL DYSPLASIA GENES ARE ASSOCIATED WITH OSTEOARTHRITIS

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Purpose: To find novel genes involved in osteoarthritis (OA) by studying common genetic variation in genes that have previously been identified to cause rare skeletal (dysplasia) syndromes, for example achondroplasia or Stickler syndrome.

Methods: All known genes causing skeletal (dysplasia) syndromes were selected based 2 criteria: 1. A list of genes selected from the

International nosology and classification of genetic skeletal disorders and 2. A systematic search in the OMIM (a database of human genes and genetic disorders). For all selected genes, we explored the common SNPs arising from the haplotype map of the human genome (HapMap). A meta-analysis of data from 8 cohorts was performed for these SNPs for hip OA (5244 cases, 17836 controls) and knee OA (5753 cases, 18498 controls). In addition, these SNPs were studied for association with a bilateral DIP OA (2007 cases, 3895 controls) and CMC OA (2017 cases, 3885 controls) within the Rotterdam Study-I. An association was declared significant after using FDR correction for multiple testing.

Results: In total, 142 genes involved in skeletal dysplasia syndromes were selected and 2766 independent SNPs were examined for association with OA. For knee OA, we observed no associations that passed the significance threshold. For hip OA, an association was found with 2 independent SNPs within the *COL11A1* gene (rs1241164, $p=1.5\times 10^{-5}$, and rs7517682, $p=1.9\times 10^{-5}$). *COL11A1* is a minor fibrillar collagen and adds structure and strength to connective tissue. Rare mutations in this gene cause some forms of Stickler syndrome. In addition, a low frequent variant (allele frequency 3%) located in the *TBX5*-gene was associated with hip OA (rs2114325, $p=2.7\times 10^{-5}$). *TBX5* is a transcription factor involved in the regulation of developmental processes and mutations in this gene cause developmental limb disorders. For bilateral CMC-OA, we found an association with a common variant in the *COL10A1* gene (rs11153598, $p=2.3\times 10^{-5}$), mutations in which are known to cause Schmid type metaphyseal chondrodysplasia.

Conclusions: There is evidence that genes involved in rare skeletal syndromes are also involved in OA. Further replication is ongoing to confirm the role of common genetic variation in these genes in OA susceptibility.

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THE RELATIONSHIP BETWEEN DELAYED GADOLINIUM-ENHANCED MRI OF MEDIAL TIBIOFEMORAL CARTILAGE (dGEMRIC) AND MEDIAL MENISCAL PATHOLOGY IN A SAMPLE OF MIDDLE-AGED WOMEN: A 1-YEAR FOLLOW-UP STUDY USING 3.0T MRI

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Purpose: To evaluate the relationship between cartilage compositional changes assessed by delayed gadolinium-enhanced MRI of medial tibiofemoral cartilage (dGEMRIC) and medial meniscal pathology in a sample of middle-aged women, over a 1-year period using 3.0T MRI.

Methods: A total of 148 women aged ≥ 40 years were included in this longitudinal observational study of knee osteoarthritis (mean age 56.8 ± 8.7 ; mean BMI 29.3 ± 7.5 ; radiographic osteoarthritis 37.9%). 3.0T MRI of the knee was performed at baseline (BL) and 12 months follow-up (FU). T2-weighted fat-suppressed sequences were acquired for meniscal morphology assessment. Three-dimensional inversion recovery-prepared spoiled gradient recalled echo sequences 90 minutes after intravenous injection of gadolinium (Gd-DTPA²⁻) were acquired for dGEMRIC assessment. BL medial meniscal pathology was scored as follows: 0 (normal), 1 (intra-substance meniscal signal changes), 2 (single tears), and 3 (complex tears/maceration). Assessment of dGEMRIC was performed at BL and FU in the central medial femur (cMF), the medial tibial plateau (MT) and the posterior medial femur (pMF) subregions of the medial tibiofemoral compartment. Analysis of covariance was used to examine if BL and FU dGEMRIC values in matched subregions differed in regard to BL medial meniscal damage severity using normal medial menisci (grade 0) as the reference group.

Results: At BL, 62 (41.9%) medial menisci were normal (grade 0), 59 (39.9%) had grade 1 changes, 12 (8.1%) had grade 2 lesions, and 15 (10.1%) had grade 3 lesions. The mean dGEMRIC values for each medial tibiofemoral region and each medial meniscal grade at BL and

FU are displayed in Table 1. At both BL and FU, medial tibiofemoral compartments with grade 3 meniscal lesions showed significantly decreased dGEMRIC values (less proteoglycan content) at the cMF subregion compared with values at the cMF subregions of compartments with normal menisci. Differences in dGEMRIC values at the cMF subregion between grade 3 vs. grade 0 menisci were -119.1 ± 34.2 ms at BL ($p=0.03$) and -120.3 ± 35.2 ms at FU ($p=0.04$). There were no significant differences in dGEMRIC values in compartments with grade 1 meniscal changes or grade 2 meniscal lesions when compared with the reference group (Table 2).

| Time Point | Predictors | cMF | | | | | MT | | | | | pMF | | | | |
|------------|-----------------|-----|--------|--------|-----|-----|-----|--------|--------|-----|------|-----|--------|--------|-----|-----|
| | | N | Mean | SD | Min | Max | N | Mean | SD | Min | Max | N | Mean | SD | Min | Max |
| Baseline | Medial Meniscus | 148 | 581.08 | 122.23 | 263 | 978 | 148 | 563.05 | 102.26 | 300 | 818 | 148 | 606.46 | 130.03 | 309 | 954 |
| | Grade 0** | 62 | 576.98 | 103.57 | 338 | 862 | 62 | 553.02 | 90.16 | 339 | 814 | 62 | 592.45 | 108.93 | 317 | 930 |
| | Grade 1 | 59 | 612.16 | 137.89 | 263 | 978 | 59 | 598.31 | 108.58 | 300 | 818 | 59 | 642.14 | 143.16 | 309 | 954 |
| | Grade 2 | 12 | 584 | 107.9 | 390 | 759 | 12 | 537.5 | 94.6 | 370 | 702 | 12 | 597.5 | 145.39 | 359 | 950 |
| | Grade 3 | 15 | 475.53 | 80.57 | 308 | 622 | 15 | 488.6 | 80.57 | 354 | 640 | 15 | 533.53 | 112.53 | 358 | 740 |
| 1-year | Medial Meniscus | 148 | 599.05 | 126.18 | 318 | 905 | 148 | 611.61 | 107.31 | 351 | 1032 | 148 | 629.09 | 118.11 | 367 | 969 |
| | Grade 0** | 62 | 599.5 | 113.39 | 318 | 905 | 62 | 612.29 | 93.03 | 363 | 835 | 62 | 618.47 | 118.3 | 367 | 926 |
| | Grade 1 | 59 | 633.71 | 129.68 | 344 | 886 | 59 | 626.44 | 115.76 | 375 | 1032 | 59 | 649.51 | 120.18 | 392 | 969 |
| | Grade 2 | 12 | 559.42 | 103.83 | 370 | 720 | 12 | 596.42 | 114.88 | 450 | 825 | 12 | 622.25 | 117.73 | 393 | 776 |
| | Grade 3 | 15 | 492.6 | 120.23 | 343 | 769 | 15 | 562.6 | 116.64 | 351 | 797 | 15 | 598.2 | 107.06 | 441 | 818 |

Table 1. The mean values of dGEMRIC indices* at each grade of meniscal morphology and signal at baseline and 1-year follow-up. * Values in milliseconds. ** Reference group. cMF = central medial femur; MT = medial tibial plateau; pMF = posterior medial femur; SD = standard deviation.

| Region | Medial meniscus (grades) | Differences in dGEMRIC* (SD) | | p-value |
|--------|--------------------------|------------------------------|--------------|---------|
| | | 1 vs. 0 | 2 vs. 0 | |
| cMF | BL | 39.81 (19.56) | 8.38 (34.63) | 0.67 |
| | | | | 1.00 |
| | | -119.08 (34.20) | | 0.03** |
| | 1-year | 44.40 (21.18) | | 0.62 |
| | | -26.15 (37.07) | | 0.99 |
| MT | BL | -120.33 (35.23) | | 0.04** |
| | | | | |
| | | 47.32 (17.50) | | 0.24 |
| | 1-year | -10.22 (32.30) | | 1.00 |
| | | -44.42 (30.72) | | 0.95 |
| pMF | BL | 9.49 (18.14) | | 1.00 |
| | | -10.12 (33.06) | | 1.00 |
| | | -47.35 (31.55) | | 0.94 |
| | 1-year | 48.30 (22.97) | | 0.62 |
| | | 5.05 (39.66) | | 1.00 |

Table 2. Differences in dGEMRIC values at each subregion and each time point. * Values in milliseconds. ** Statistically significant defined as $p<0.05$. cMF = central medial femur; MT = medial tibial plateau; pMF = posterior medial femur; SD = standard deviation; BL = baseline.

Conclusions: In this sample of middle-aged women, alterations in cartilage matrix composition as assessed by dGEMRIC had a significant relationship with high grade damage of the medial meniscus at both BL and FU assessments. No significant changes in cartilage matrix composition were observed in compartments with only intra-substance meniscal signal changes or meniscal single tears.